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Infant Feeding in Relation to the Risk of Advanced Islet Autoimmunity and Type 1 Diabetes in Children With HLA-Conferred Disease Susceptibility to Type 1 Diabetes: A Cohort Study

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Abbreviations: DIPP Study, the Finnish Type 1 Diabetes Prediction and Prevention Study; *HLA-DQB1*, Major Histocompatibility Complex, Class II, DQ Beta

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Abstract

The aim was to study the association of breastfeeding, age at introduction of foods and food diversity in infancy with advanced islet autoimmunity and type 1 diabetes. In the prospective Finnish Type 1 Diabetes Prediction and Prevention Study, 5,915 newborn infants with increased susceptibility to type 1 diabetes, recruited in 1996-2004, were included. Children were followed at 3-12 month intervals for 4 islet autoantibodies and for type 1 diabetes up to the age of 15 years. Survival models were used for statistical analyses. Breastfeeding, age at introduction of any new food, or food diversity were not associated with advanced islet autoimmunity or type 1 diabetes in the cohort. Early introduction of solid foods was associated with increased risk of developing advanced islet autoimmunity in up to the age of 3 years (HR 2.33; 95% CI 1.39, 3.91 for <3 months and HR 2.18; 95% CI 1.38, 3.47 for 3-4 months vs. >4 months) but not in longer follow-up (*P* value for interaction=0.046). Similar results were observed for age at introduction of roots, cereals, egg and meat with advanced islet autoimmunity. To conclude, no consistent long-term associations between infant feeding and advanced islet autoimmunity or type 1 diabetes were observed.

Since the gut microbiota and immune system are immature at birth, very early introduction of supplemental foods have been implicated to trigger immune-mediated processes that may lead to type 1 diabetes (1-5). Early introduction of root vegetables, fruits or berries, or cereals have been inconsistently associated with islet autoimmunity in prospective studies in children with increased susceptibility to type 1 diabetes (2, 4, 6-9). The inconsistent results may be related to association-modifying effects of genes and breastfeeding (10-12).

Only a few prospective studies have reported age at introduction of foods and risk of clinical type 1 diabetes (7, 8, 12, 13), mostly in children carrying genetic susceptibility (7, 8, 12). In the US-based DAISY Study, early (<4 months) and late (≥6 months) introduction of solid foods was associated with increased risk of type 1 diabetes (12). In the Norwegian MIDIA Study, no significant associations were observed, except for a protective association of breastfeeding for 12 months or longer (7). The German BABYBIAB/BABYDIET Study reported an association between early (<3 month) introduction of gluten containing cereals and type 1 diabetes (8).

Higher food diversity could, in theory, modify the development of gut microbiota and immune system towards a healthier direction, and therefore decrease the risk of developing type 1 diabetes (1, 14). The association between higher food diversity in infancy and decreased risk of childhood allergic diseases (15) encouraged us to study, whether food diversity would also associate with the risk of developing type 1 diabetes.

We previously reported the associations between breastfeeding and age at introduction of foods with the development of advanced islet autoimmunity (4, 6). Now with a larger study population and longer follow-up, the primary aims were to study whether breastfeeding and age at introduction of complementary foods or food diversity in infancy are associated with advanced islet autoimmunity or type 1 diabetes. The secondary aims were to study, whether follow-up time and selected type 1 diabetes related genes modify the associations between infant dietary exposures and advanced islet autoimmunity or type 1 diabetes.

METHODS

Study Design and Population

This study is part of the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) Study, which is a large population-based birth cohort study of children with Major Histocompatibility Complex, Class II (HLA)-conferred susceptibility to type 1 diabetes (16). In the DIPP Nutrition Study, 7782 children born in the Tampere and Oulu University Hospitals between September 1996 and September 2004 were invited for follow-up (Web Figure 1). Children with genotypes *HLA-DQB1*02/*03:02* and *DQB1*03:02/*x (x stands for alleles other than *DQB1*02* or *DQB1*0602/3* until March 1997 and other than *DQB1*02* or *DQB1*06:02* thereafter) were eligible for DIPP follow-up. The children were invited to study visits in 3 to 12 months intervals until the age of 15 years or until the manifestation of type 1 diabetes. The inclusion criteria for the present report was having data on early feeding and islet autoimmunity and/or type 1 diabetes. To test the potential gene-modifying effects of *INS* and *PTPN22*, we used a nested case-control setting within the cohort. For 295 cases with advanced islet autoimmunity (in September 2012), we randomly selected 2 controls matched with the cases for the date of birth within 3 months, sex, HLA-genotype and area of birth, who were islet cell antibody-negative and diabetes-free at the time the case turned out to be a case. Parents gave their written informed consent for genetic testing of their newborn from cord blood sample and for participation in the follow-up. The study adheres to the Declaration of Helsinki, and the local ethics committees have approved the study protocol.

Dietary Assessment

Parents completed age-specific dietary questionnaires and an “age at introduction of new foods” form at home. The form and the questionnaires were checked by a trained study nurse at study visits at 3, 6, 12, 18 and 24 months (4). The duration of breastfeeding, use of infant formulas, vitamin supplements and age at introduction of complementary foods were asked about. The duration of

exclusive breastfeeding was defined as the age when consuming any food or drink other than breast milk, water or dietary supplements, for the first time. Early exposure to any infant formula or cow's milk based formula at hospital was considered as end of exclusive breastfeeding and first use of cow's milk, respectively. Duration of any breastfeeding was the age, when child received breast milk for the last time. Introduction of a new food (cow's milk or cow's milk based infant formula (combined); potatoes; carrots; turnip; fruits or berries (combined); cereals (rye, wheat, oats, or barley combined); other cereals; meat; fish; egg; cabbage; spinach or beetroot (combined); and lettuce) was recorded with an accuracy of 0.5 months. The food diversity was the sum of these 13 foods/food groups that the child had started to consume. Age at introduction of solid foods was the first introduction of any of the following: roots, fruits or berries, cereals, other cereals, meat, fish, egg, cabbage, spinach, beetroot and lettuce. Age at introduction of roots included carrots, potatoes and turnip.

Advanced Islet Autoimmunity, Type 1 Diabetes and Progression to Type 1 Diabetes

Children were screened for islet cell antibodies at 3 to 12-month intervals as described before (4). When a child seroconverted to positivity for islet cell antibodies for the first time, all preceding and subsequent samples from that participant were analyzed for insulin autoantibodies, glutamic acid decarboxylase and islet antigen-2 antibodies. Islet cell antibodies were quantified by a standard indirect immunofluorescence method, insulin autoantibodies, glutamic acid decarboxylase and islet antigen-2 antibodies with specific radiobinding assays. Advanced islet autoimmunity was defined as repeated positivity for islet cell antibody and at least 1other autoantibody, excluding transplacentally transferred autoantibodies. Children with type 1 diabetes were included in the group of children with advanced autoimmunity. Type 1 diabetes was defined according to World Health Organization criteria (17). Risk of progression to type 1 diabetes was assessed among children with repeated positivity to at least 1 islet autoantibody (progression cohort). The number of cases for the whole cohort were updated between May 2014 and May 2015.

Genetic Methods

HLA-DQ was genotyped using panels of sequence-specific oligonucleotide probes, as described before (18). Genotypes *HLA-DQB1(*02/*03:02)* represent "high" and *HLA-DQB1*03:02*/x (x ≠*02, *03:01, *06:02*) "moderate" risk for type 1 diabetes. *INS*-23 A/T (rs689) and *PTPN22* 1858C/T (rs2476601) were genotyped using the Sequenom platform, or using the TaqMan SNP genotyping array, with *INS* AA and *PTPN22* TT/CT regarded as the risk genotypes for type 1 diabetes (19).

Demographic and Perinatal Characteristics

Information on maternal vocational education and age, any type of diabetes in first-degree relative (=familial diabetes), and offspring sex was collected with a questionnaire after delivery. Information on the number of previous deliveries, gestational age, number of fetuses, birth weight and length (ponderal index was calculated as kg/m^3), and maternal smoking during pregnancy was obtained from the medical birth registers of the university hospitals.

Statistical Methods

To study the associations between characteristics of the participants and dietary exposures with advanced islet autoimmunity, a piecewise linear log-hazard survival model was used (Web Appendix 1). The risk of type 1 diabetes in the whole cohort and in the progression cohort, were assessed with Cox proportional hazards regression analysis. For progression to the type 1 diabetes outcome, delayed entry into the risk set was incorporated into the model, i.e. subjects enter the analysis at the age of autoantibody positivity and exit at their event/censoring age. In the Cox models, dependence among siblings was taken into account by performing a marginal analysis with a working independence assumption and a robust sandwich estimator of variance.

Age at introduction of each food as well as duration of exclusive and any breastfeeding were categorized into thirds, and the last third was used as the reference category. As all children are

unexposed at birth, the children shifted to their exposure category at the time of the introduction. Food diversity was categorized into 3 or 4 classes based on variable distributions, and the last class was used as the reference category. Results of the main analysis were adjusted for HLA risk genotype (high/moderate), familial diabetes (yes/no), child sex (boy/girl) and maternal education (none, vocational, secondary vocational, university studies or degree). The unadjusted sensitivity analyses were done for the breastfeeding variables: 1) division of the exposure variable into quarters, and 2) disregarding the hospital exposure to infant formula when the exclusive breastfeeding was divided in thirds.

The proportionality of the hazards was tested by adding linear interaction terms of the dietary exposures with time to the models of advanced islet autoimmunity and type 1 diabetes. If there was any indication of an interaction *(P* < 0.05), then separate results at age categories 0-3, 3.1-6 and >6 years were obtained to illustrate such time-varying effect. To study whether the HLA risk genotype modified the associations between dietary exposures and outcomes, we added interaction terms to the models. Separate results for HLA risk genotype categories are presented, if the interaction was significant *(P* < 0.05). Finally, conditional logistic regression analysis with interaction terms was used to study whether *INS* and *PTPN22* genotypes modified the associations in the nested case-control setting.

SAS software version 9.3 (SAS Institute, Cary, NC, USA) was used in the analyses. Statistical significance was set at 2-sided *P* < 0.05.

RESULTS

Of the 6,081 participants enrolled, 5,915 had data on early feeding (Web Figure 1). Within these participants, the median (interquartile range) number of antibody measurements was 11 (5, 16) per child. Altogether, 359 children had developed advanced islet autoimmunity or type 1 diabetes at a median age of 4.0 (2.0, 7.2), and 188 children had developed type 1 diabetes at a median age of 6.0

(3.8, 9.2) years. There were 975 children with repeated positivity for at least 1 islet autoantibody and 154 of them progressed to type 1 diabetes. Among them, the median (interquartile range) duration of the preclinical period was 3.6 (1.9, 6.1) years after the first positivity to any autoantibody. The drop-out rates among the 5,915 participants who were included in the analysis at 1 and 5-year follow up were 10.5% and 34.6%, respectively.

Male sex, the high-risk HLA-DQB1 genotype and familial diabetes were associated with increased risk of developing advanced islet autoimmunity and type 1 diabetes (Table 1). Maternal age and gestational age were not associated with advanced islet autoimmunity or type 1 diabetes (data not shown). Higher maternal education was associated with decreased risk of developing advanced islet autoimmunity (Table 1) but with increased risk of progressing to type 1 diabetes (Web Table 1).

Median (interquartile range) duration of exclusive and any breastfeeding was 1.4 (0.2, 3.5) and 7.0 (3.0, 10.0) months, respectively. The earliest supplementary foods were infant formulas, root vegetables (including potatoes), fruits or berries, and cereals, which were introduced at the median age of 1.4, 3.5, 4.0, and 5.0 months, respectively. The median age at introduction of any solid food was 3.5 (3.0, 4.0) months.

Age at Introduction of Foods and Risk of Advanced Islet Autoimmunity and Type 1 Diabetes

Duration of breastfeeding or age at introduction of any new foods were not associated with development of advanced islet autoimmunity, type 1 diabetes (Table 2) or progression to type 1 diabetes among children with repeated autoantibody positivity (Web Table 2) over the 15-year follow-up. These associations were not affected by adjustment for HLA genotype, familial diabetes, child's sex and maternal education (Change in hazard ratios (HR) due to adjustment varied between 0.0 and 0.18). Breastfeeding at the time of introduction of each food, adjusted with age at introduction of each food was not associated with risk of developing islet autoimmunity, type 1 diabetes or progression to type 1 diabetes.

Altogether 181 children had an early exposure to infant formula but were not in the first third of exclusive breastfeeding when early exposure was disregarded. Duration of exclusive breastfeeding, when hospital exposure to infant formula was disregarded, was not associated with advanced islet autoimmunity or type 1 diabetes. Shorter exclusive breastfeeding and any breastfeeding, when divided in quarters, were associated with increased risk of advanced islet autoimmunity, but not type 1 diabetes (Web Table 3).

For the risk of advanced islet autoimmunity, we observed a statistically significant interaction for follow-up time with age at introduction of roots ($P = 0.02$), wheat, rye, oats or barley combined ($P = 0.03$), egg ($P = 0.008$), meat ($P = 0.008$) and solid foods ($P = 0.046$) (Table 3). In general, early introduction of these foods was associated with developing advanced islet autoimmunity before but not after the age of 3 years (Table 3). No other follow-up time-interactions were observed for age at introduction of foods and the risk of advanced islet autoimmunity or type 1 diabetes.

The HLA-genotype modified the associations between the age at introduction of roots or any solid foods, and the risk of developing advanced islet autoimmunity, such that introduction of roots and solid foods at the age of 3-4 months versus after 4 months of age was associated with advanced islet autoimmunity only in children with the high-risk genotype (Table 4).

The *INS*- genotype modified the association between age at introduction of meat and risk of advanced islet autoimmunity, such that early introduction of meat (OR: 3.08, 95% CI: 1.06, 8.95 for the first third and OR: 1.02, 95% CI: 0.55, 1.88 for the middle third versus the third third) was associated with advanced islet autoimmunity in children with the *INS* AT/TT genotype but not in those carrying the *INS* AA genotype (OR: 0.60, 95% CI: 0.30, 1.21 for the first third and OR: 0.69, 95% CI: 0.48, 1.00 for the second third), *P* value for interaction = 0.046.

The *PTPN22*- genotype modified the association between age at introduction of fish and risk of advanced islet autoimmunity with the following odds ratios (OR: 1.65, 95% CI: 0.74, 3.68 for the

first third and OR: 0.64, 95% CI: 0.34, 1.20 for the middle third versus the third third) in children with *PTPN22* TT/CT genotype and (OR: 0.94, 95% CI: 0.56, 1.57 for the first, and OR: 1.37, 95% CI: 0.91, 2.05 for the middle third) in children with the *PTPN22* CC genotype, *P* value for interaction = 0.006.

We observed no other modifying effects of HLA-, *INS*- or *PTPN22*-genotypes on the associations between age at introduction of foods and the outcomes.

Food Diversity and Risk of Advanced Islet Autoimmunity and Type 1 Diabetes

Food diversity at age 3, 4, 6 or 12 months was not associated with the development of advanced islet autoimmunity or type 1 diabetes in the cohort, (Figure 1) nor with progression to type 1 diabetes (Web Table 4). Adjustment with potential confounders did not change the results.

We found no modifying effects of follow-up time or HLA-genotype on the associations between food diversity and advanced islet autoimmunity or type 1 diabetes. There was no indication of modifying effect of *INS* and *PTPN22*-genotypes on the associations between food diversity and advanced islet autoimmunity.

DISCUSSION

In this large prospective birth cohort of children with increased genetic risk for type 1 diabetes, breastfeeding, age at introduction of foods or food diversity in infancy were not consistently associated with developing advanced islet autoimmunity or type 1 diabetes. Further, infant feeding was not associated with progression to type 1 diabetes in children with persistent autoantibody positivity.

This study have several strengths: First, the large study population with a higher number of children with advanced islet autoimmunity and type 1 diabetes than any previous prospective study, and a long follow-up time enabled us to study associations with sufficient statistical power. Second,

information on carefully and consistently assessed early diet was collected before the development of advanced autoimmunity or type 1 diabetes, reducing reporting bias. Finally, we were able to assess the possible modifying effects of follow-up duration and essential type 1 diabetes risk genotypes.

The main limitation is that the amount of foods consumed at the first exposures, or the continuity of use was not available. The study population consisted of children at increased genetic risk for type 1 diabetes, and whether these findings apply to the general population, is not known.

In our previous reports, early exposure to root vegetables was associated with development of advanced islet autoimmunity (4, 6). In the present report with longer follow-up and larger number of cases with advanced islet autoimmunity, the associations were of the same direction but no more statistically significant. We observed time-interaction for age at introduction of some foods, and in general, early introduction of these foods had stronger association with advanced islet autoimmunity with shorter than longer follow-up. However, in general, we observed no consistent associations between early feeding and clinical type 1 diabetes. These results together indicate that if early feeding plays a role in the disease process of type 1 diabetes, the role may be most important in the islet autoimmunity that develops at very young age, and the association may dilute over time.

Only 3 other prospective studies have explored the associations between early feeding and islet autoimmunity and clinical type 1 diabetes. In the DAISY Study both early (≤3 month) and late (≥7 months) introduction of any cereal and early introduction of rice were associated with increased risk of islet autoimmunity (2). In the same population both early (<4 month) and late (≥6 months) introduction of solid foods, late introduction of any cereal and rice/oat, and early introduction of fruit were associated with increased risk of type 1 diabetes (12). In the BABYDIAB/BABYDIET Study, early (<3 month) introduction of gluten containing cereals was associated with increased risk

of islet autoimmunity (2) and type 1 diabetes (8). The MIDIA Study found no association between age at introduction of complementary foods and risk of islet autoimmunity or type 1 diabetes (7). In comparison to previous studies, the current study has much higher number of children with type 1 diabetes and infant feeding data (n=188) compared to the DAISY (n=53), MIDIA (n=25) and BABYDIAB/BABYDIET (n=74) studies (6-8, 12). The slightly different data collection methods and categorization of infant feeding data, different inclusion criteria and country-specific infant feeding patterns may explain the variable results.

We found no association between duration of exclusive or any breastfeeding with advanced islet autoimmunity or type 1 diabetes in the main analyses. However, analyses with quarter categorization showed that shorter breastfeeding was associated with increased risk of advanced islet autoimmunity but not that of type 1 diabetes. These findings together with other studies (2, 6) demonstrate a potential ~~weak~~ protective association of breastfeeding with islet autoimmunity. To analyze the risk of advanced islet autoimmunity or type 1 diabetes in breastfed versus non-breastfed children was not possible due to the small number of non-breastfed children.

To our knowledge, this was the first study to explore the associations between food diversity in infancy and the risk of islet autoimmunity or type 1 diabetes. Our results indicate that food diversity may not be associated with the disease process leading to type 1 diabetes.

We found that introduction of roots and solid foods at age 3-4 months were associated with increased risk of developing advanced islet autoimmunity in HLA high-risk children but no such association was observed in moderate-risk children. In previous studies, based on limited number of children, there has been some indication of potential differences in the associations between age at introduction of cereals (2) or gluten containing cereals (3) by HLA-DR genotype, so that high-risk children with early introduction of cereals seemed to have the highest risk of islet autoimmunity. To our knowledge, this was the first study to report the modifying effect of *INS* and *PTPN22* genotypes on the associations between age at introduction of solid foods and food diversity with islet

autoimmunity. Only weak interactions of *INS* and *PTPN22* genotypes and age at introduction of meat and fish, respectively, on the risk of advanced islet autoimmunity were observed. The genetic interaction and subgroup analyses were exploratory and showed no consistent pattern on food groups or age at introduction of foods and the risk of advanced islet autoimmunity or type 1 diabetes. These findings need confirmation from other studies before further conclusions.

Taken our present and previous results (4, 6) as well as other studies (7, 8, 12) together, early introduction of foods and breastfeeding may play role in the disease process of type 1 diabetes. However, the inconsistent results may be due to the several simultaneous and subsequent exposures that may blur the associations. These include child's genotype (10) and viral infections (20) as well as intakes of probiotics (21), vitamin D (22), cow's milk (10, 23), and marine fatty acids (24). Finally, the disease etiology can be heterogeneous regarding the type of the first islet autoantibodies and progression rate to type 1 diabetes, and infant feeding may modify some immune processes more than others. Therefore, some existing weak associations may have escaped statistical significance in the present study.

To conclude, age at introduction of foods was not associated with clinical type 1 diabetes. We reported for the first time associations of food diversity and advanced islet autoimmunity and type 1 diabetes with no significant associations.

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Table 1. Characteristics and Unadjusted Hazard Ratios (HR) and 95% Confidence Intervals (95% CI) for Advanced Islet Autoimmunity and Type 1 Diabetes in 5,915 Children With Increased Genetic Susceptibility for Type 1 Diabetes Recruited in 1996-2004, DIPP Nutrition Study, Finland.

Characteristic	All Children (*n* = 5,915)	Advanced Islet Autoimmunity (*n* = 359)			Type 1 Diabetes (*n* = 188)		
	No.	No.	HR	95% CI	No.	HR	95% CI
Child sex							
Boys	3,146	216	1.37	1.10, 1.71	113	1.33	1.00, 1.78
Girls	2,769	143	1		75	1	
P value				0.005[a]			0.05[b]
HLA-DQB1risk[c]							
High	1,149	121	2.25	1.78, 2.84	68	2.39	1.77, 3.24
Moderate	4,766	238	1		120	1	
P value				0.001[a]			0.001 [b]
Familial diabetes							
Yes	343	43	2.15	1.52, 3.04	27	2.73	1.78, 4.20
No	5,324	307	1		157	1	
Missing	248	9			4		
P value				0.001[a]			0.001 [b]
Maternal vocational education[d]							
None	386	36	1		17	1	
Vocational	1,584	85	0.49	0.32, 0.74	41	0.58	0.32, 1.06
School or Course							
Secondary vocational education	2,495	138	0.46	0.31, 0.68	68	0.62	0.36, 1.08
University	1,259	91	0.63	0.42, 0.95	57	1.04	0.59, 1.84
Studies or Degree							
Missing	191	9			5		
P value				0.001[a]			0.07 [b]
Ponderal index[e]							
Q_1 < 26.1	1,470	95	1		47	1	
Q_2 26.1–27.7	1,475	91	0.97	0.72, 1.30	53	1.12	0.76, 1.67
Q_3 27.8–29.3	1,465	88	0.92	0.68, 1.25	47	1.01	0.67, 1.51
$Q_4 \geq 29.4$	1,460	81	0.85	0.63, 1.16	38	0.81	0.53, 1.24
Missing	45	4			3		
P value				0.77[a]			0.50[b]
Maternal smoking during pregnancy							
Yes	570	31	1.02	0.69, 1.50	15	0.79	0.45, 1.38
No	5,146	321	1		169	1	
Missing	199	7			4		
P value				0.92[a]			0.41[b]
Number of siblings[d], %							
0	2,675	174	1		92	1	
1	1,773	109	0.89	0.69, 1.14	60	0.98	0.71, 1.35
2or more	1,277	68	0.75	0.56, 1.01	32	0.73	0.49, 1.08
Missing	190	8			4		
P value				0.15[a]			0.26[b]

Abbreviations: CI, confidence interval; HLA-DQB1, Major Histocompatibility Complex Class II DQ Beta; HR, hazard ratio; Q_{1-4}, quarter 1-4.

[*a] *P* values are from piecewise linear log-hazard survival model (Log likelihood test);
[b] *P* values from Cox regression analysis (Wald test);
[c] High risk genotype *HLA-DQB1(*02/*03:02):* Moderate risk genotypes *HLA-DQB1(*03:02/x); x ≠ *02, *03:01,*06:02)*
[d] at the time of birth
[e] Ponderal index was calculated as birth weight in kilograms divided by birth length in meters in 3rd power (kg/m^3).

Table 2. Duration of Breastfeeding, Age at Introduction of Foods and Unadjusted Hazard Ratios (HR) and 95% Confidence Intervals (95% CI) for Advanced Islet Autoimmunity and Type 1 Diabetes in Children With Increased Genetic Susceptibility for Type 1 Diabetes, DIPP Nutrition Study, Finland, 1996-2015.

Age (months)	All children (*n* = 5,915)	Advanced Islet Autoimmunity (*n* = 359)			Type 1 Diabetes (*n* = 188)		
	No.	No.	HR	95% CI	No.	HR	95% CI
Exclusive breastfeeding							
<0.5	1,860	106	1.01	0.77, 1.32	55	0.86	0.60, 1.22
0.5–2.99	2,103	136	1.17	0.91, 1.52	65	0.88	0.63, 1.23
>2.99	1,945	117	1		68	1	
Missing	7	0			0		
P value				0.39[a]			0.64[b]
Any breastfeeding							
<5.0	1,896	119	1.31	1.00, 1.71	55	0.92	0.63, 1.33
5.0–9.0	1,864	117	1.14	0.87, 1.50	64	1.09	0.76, 1.56
>9.0	1,791	110	1		56	1	
Missing	364	13			13		
P value				0.15[a]			0.64[b]
Cow's milk[c]							
< 0.9	1,841	115	1.10	0.84, 1.45	56	0.94	0.64, 1.36
0.9–4.0	2,185	126	1.02	0.78, 1.34	69	1.00	0.69, 1.42
>4.0	1,755	109	1		55	1	
Missing	134	9			8		
P value				0.75[a]			0.93[b]
Fruits or berries							
<3.5	1,586	93	1.25	0.93, 1.68	48	1.02	0.69, 1.52
3.5–4.0	2,290	150	1.28	0.99, 1.67	76	1.13	0.79, 1.61
4.0	1,746	100	1		51	1	
Missing	293	16			13		
P value				0.14[a]			0.76[b]
Roots[d]							
<3.0	1,163	66	1.41	0.98, 2.03	34	1.05	0.64, 1.72
3.0–4.0	3,375	217	1.40	1.04, 1.89	111	1.19	0.79, 1.80
>4.0	1,090	60	1		30	1	
Missing	287	16			13		
P value				0.07[a]			0.63[b]
Wheat, rye, oats or barley							
<5.0	968	51	1.02	0.71, 1.46	21	0.68	0.40, 1.14
5.0–5.5	3,188	205	1.19	0.91, 1.56	108	1.07	0.75, 1.52
>5.5	1,386	85	1		44	1	
Missing	373	18			15		
P value				0.35[a]			0.16[b]
Egg							
<8.0	1,334	84	1.19	0.88, 1.61	48	1.20	0.80, 1.80
8.0–11.0	2,243	141	1.19	0.90, 1.55	68	1.02	0.70, 1.48
>11.0	1,702	105	1		51	1	
Missing	636	29			21		
P value				0.40[a]			0.60[b]
Fish							
<6.0	1,132	74	1.33	0.96, 1.83	37	1.17	0.75, 1.83
6.0–9.0	2,652	164	1.18	0.90, 1.55	87	1.19	0.81, 1.73
>9.0	1,543	93	1		43	1	

Missing	588	28			21		
P value				0.21[a]			0.66[b]
Meat							
<5.0	470	30	1.16	0.76, 1.78	13	0.82	0.45, 1.50
5.0–5.5	3,372	199	1.00	0.78, 1.28	104	0.93	0.67, 1.28
>5.5	1,697	112	1		56	1	
Missing	376	18			15		
P value				0.75[a]			0.86[b]
Solid foods[e]							
< 3.0	1,566	86	1.29	0.90, 1.85	43	0.90	0.56, 1.45
3.0–4.0	3,191	206	1.38	1.00, 1.90	105	1.09	0.71, 1.66
> 4.0	896	51	1		27	1	
Missing	262	16			13		
P value				0.13[a]			0.57[b]

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]*P* values are from piecewise linear log-hazard survival model (Log likelihood test);

[b]*P* values from Cox regression analysis (Wald test);

[c]Cow's milk includes cow's milk based infant formulas as well as any other foods including cow's milk;

[d]Roots include carrots, potatoes and turnips

[e]Solid foods include roots, fruits or berries, cereals, meat, fish, egg, cabbage, spinach, beetroot and lettuce.

Table 3. Age at Introduction of Foods and Unadjusted Hazard Ratios (HR) and 95% Confidence Intervals (95% CI) for Advanced Islet Autoimmunity by Follow-up Time, DIPP Nutrition Study, Finland, 1996-2015.

Age (months)	Advanced Islet Autoimmunity									*P* value for interaction
	0-3 years			3.1-6 years			> 6 years			
	n	HR	95% CI	n	HR	95% CI	n	HR	95% CI	
Roots[a]										0.02[b]
<3.0	27	2.37	1.38, 4.07	20	1.17	0.68, 1.99	19	0.95	0.54, 1.68	
3.0–4.0	83	2.26	1.46, 3.50	66	1.15	0.78, 1.69	68	1.01	0.67, 1.53	
>4.0	15	1		19	1		26	1		
P value			< 0.001[c]			0.75[c]			0.98[c]	
Wheat, rye, oats or barley										0.03[b]
<5.0	14	1.04	0.57, 1.92	15	0.80	0.45, 1.43	22	1.12	0.66, 1.89	
5.0–5.5	82	1.82	1.25, 2.67	62	0.96	0.67, 1.38	61	0.88	0.59, 1.32	
>5.5	28	1		28	1		29	1		
P value			0.004[c]			0.75[c]			0.62[c]	
Egg										0.008[b]
<8.0	38	2.03	1.32, 3.13	26	1.03	0.65, 1.63	20	0.69	0.41, 1.16	
8.0–11.0	50	1.73	1.14, 2.61	46	1.04	0.71, 1.52	45	0.91	0.61, 1.36	
>11.0	35	1		31	1		39	1		
P value			0.02[c]			0.98[c]			0.35[c]	
Meat										0.008[b]
<5.0	8	1.14	0.53, 2.42	10	1.06	0.54, 2.07	12	1.25	0.66, 2.36	
5.0–5.5	81	1.62	1.13, 2.33	60	0.81	0.58, 1.15	58	0.71	0.49, 1.04	
>5.5	35	1		35	1		42	1		
P value			0.03[c]			0.46[c]			0.10[c]	
Solid foods[d]										0.046[b]
< 3.0	37	2.33	1.39, 3.91	23	0.93	0.55, 1.57	23	0.90	0.53, 1.53	
3.0–4.0	76	2.18	1.38, 3.47	65	1.15	0.77, 1.72	65	0.99	0.64, 1.53	
> 4.0	12	1		17	1		22	1		
P value			< 0.001[c]			0.63[c]			0.91[c]	

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]Roots include carrots, potatoes and turnips

[b]*P* values for interaction (categorized age at introduction of food*continuous follow-up time)

[c]*P* values are from piecewise linear log-hazard survival model (Log likelihood test) including interaction terms

[d]Solid foods include roots, fruits or berries, cereals, meat, fish, egg, cabbage, spinach, beetroot and lettuce.

Table 4. Age at Introduction of Roots and Solid Foods and Unadjusted Hazard Ratios (HR) and 95% Confidence Intervals (95% CI) for Advanced Islet Autoimmunity and Type 1 Diabetes by HLA-DQ genotype, DIPP Nutrition Study, Finland, 1996-2015.

	HLA Moderate risk[a]				HLA High risk[b]					HLA Moderate risk[a]			HLA High risk[b]			
		Advanced Islet Autoimmunity				Advanced Islet Autoimmunity				Type 1 Diabetes			Type 1 Diabetes			
Age, months	n total	n cases	HR	95% CI	n total	n cases	HR	95% CI	*P* value	n cases	HR	95% CI	n cases	HR	95% CI	*P* value
Roots[c]									0.001[d]							0.010[d]
<3.0	936	52	1.50	0.99, 2.27	227	14	1.11	0.52, 2.38		28	1.23	0.69, 2.19	6	0.63	0.23, 1.76	
3.0–4.0	2,741	132	1.10	0.77, 1.56	634	85	2.49	1.40, 4.42		64	0.96	0.58, 1.60	47	1.82	0.90, 3.71	
>4.0	871	45	1		219	15	1			21	1		9	1		
P value			0.12[e]				< 0.001[e]				0.56[f]			0.017[f]		
Solid foods[g]									0.002[d]							0.038[d]
< 3.0	1,266	67	1.40	0.93, 2.13	300	19	0.97	0.47, 2.00		34	1.07	0.61, 1.87	9	0.57	0.23, 1.43	
3.0–4.0	2,581	125	1.13	0.77, 1.65	610	81	2.12	1.17, 3.84		61	0.94	0.56, 1.60	44	1.40	0.68, 2.87	
> 4.0	721	37	1		175	14	1			18	1		9	1		
P value			0.23[e]				0.001[e]				0.84[f]			0.038[f]		

Abbreviations: CI, confidence interval; HLA, human leucocyte antigen; HR, hazard ratio.

[a] Moderate risk includes genotypes *HLA-DQB1(*03:02/x); x ≠ *02, *03:01, *06:02)*

[b] High risk includes genotypes *HLA-DQB1(*02/*03:02)*

[c] Roots include carrots, potatoes and turnips

[d] *P* values for interaction term (categorized age at introduction of food*HLA genotype)

[e] Overall *P* values are from piecewise linear log-hazard survival model including HLA-genotype and interaction terms (Likelihood Ratio test)

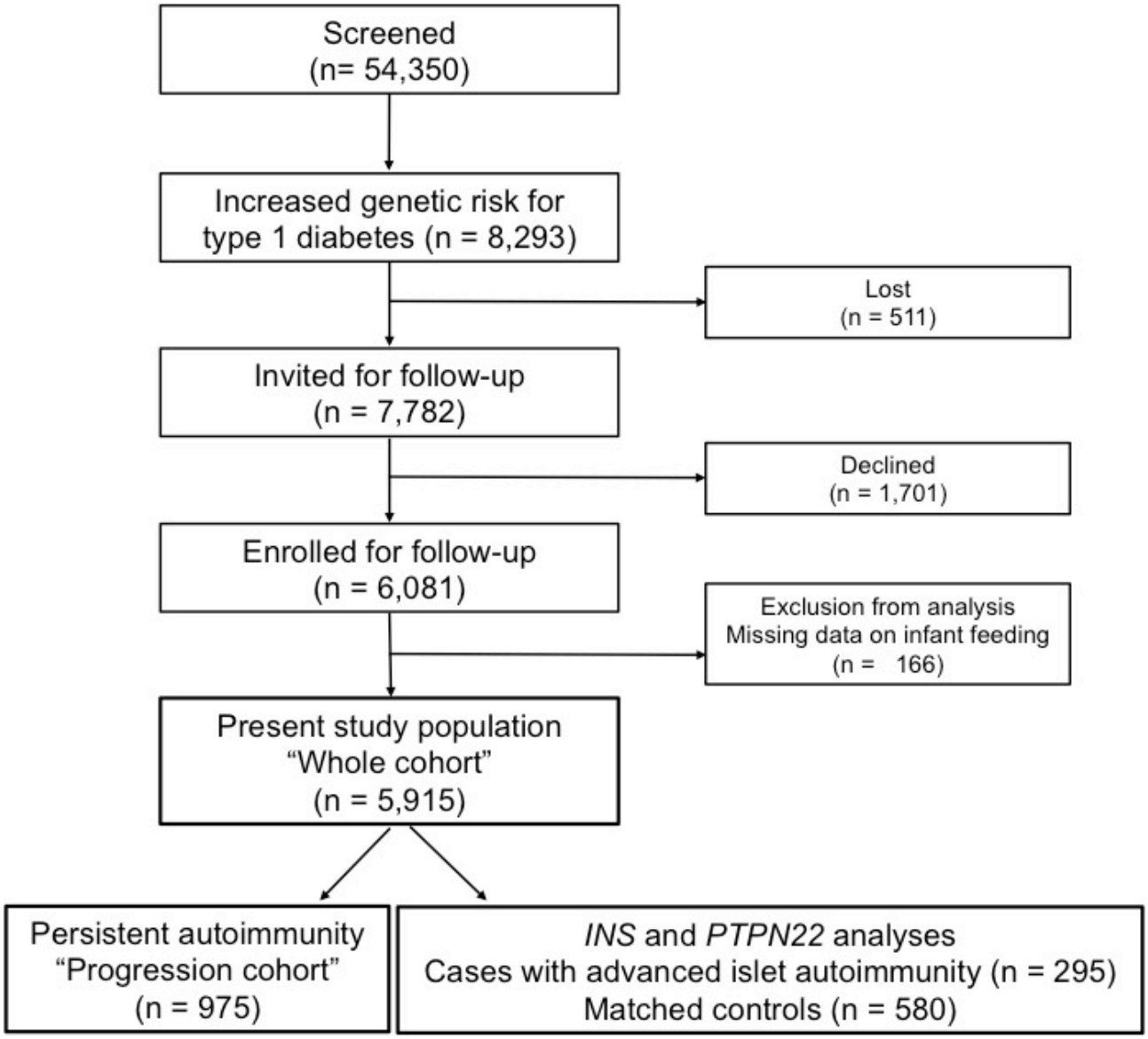
[f] Overall *P* values Cox regression analysis including HLA-genotype and interaction terms (Wald test)

[g] Solid foods include roots, fruits or berries, cereals, meat, fish, egg, cabbage, spinach, beetroot and lettuce.

Figure 1. Food Diversity at Age of 3, 4, 6, and 12 Months and the Unadjusted Hazard Ratios (95% Confidence Intervals) for Advanced Islet Autoimmunity and Type 1 Diabetes in Children With Increased Genetic Susceptibility for Type 1 Diabetes, DIPP Nutrition Study, Finland, 1996-2015.

CI, confidence interval; HR, hazard ratio; The food diversity is the sum of the following 13 foods/food groups that the child had started to consume: cow's milk or cow's milk based infant formula (combined); potato; carrot; turnip; fruits or berries (combined); cereals (rye, wheat, oats, or barley combined); other cereals; meat; fish; egg; cabbage; spinach or beetroot (combined); and lettuce. A) HRs and 95% CIs for the risk of advanced islet autoimmunity are from piecewise linear log-hazard survival model; B) HRs and 95% CIs for type 1 diabetes are from Cox regression analysis.

Web Figure 1. Flowchart of the Study Recruitment and Formation of the Present Study Population Recruited in 1996-2004, DIPP Nutrition Study, Finland.



Web Appendix 1

Piecewise Linear Log-Hazard Survival Model

Since autoantibodies were screened in 3 to 12 month intervals, the timing of the advanced islet autoimmunity is after the last negative assessment of the outcome and before the first positive assessment. Therefore, advanced islet autoimmunity outcome is interval censored, i.e. the advanced islet autoimmunity time T of the subject can't be directly observed, but can be observed to lie within some time interval. A piecewise linear log-hazard survival model, which allows a flexible estimation of the baseline hazard function (and the distribution of the event times) from the data, was used to build the model for the interval censored outcome observed at arbitrary times. The corresponding likelihood was constructed as described before (1).

To be more specific, the time scale was divided into three intervals [0,2), [2,4) and [4,∞), and linear log-hazards in the intervals were assumed. The results were not sensitive to the particular choice of intervals used. The hazard function of the model was assumed to be given by

$$log h_0(t) = \alpha + \beta_1 t + \beta_2 (t-2) I(t > 2) + \beta_3 (t-4) I(t > 4).$$

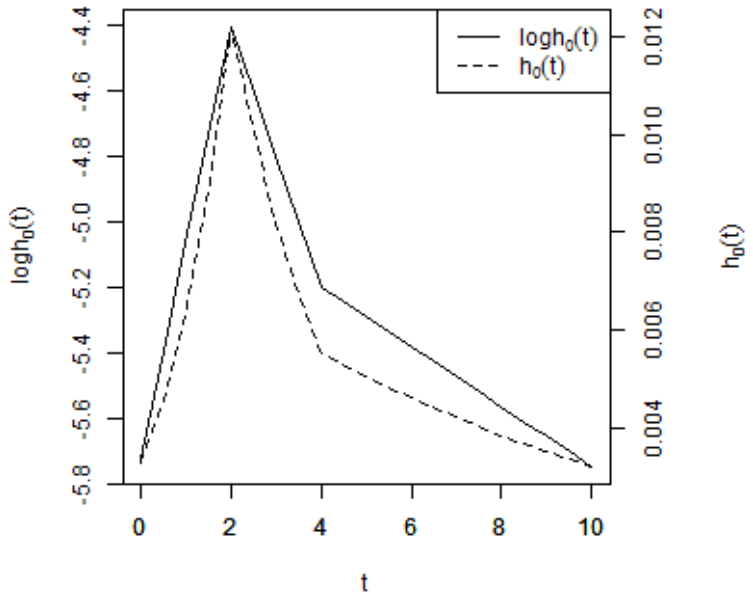
Figure S1 suggests that the hazard for advanced islet autoimmunity starts to increase from the birth and reaches the highest intensity at approximately two years of age. After that period, the hazard steadily declines to less than one third of the peak value of the hazard.

To estimate the effects of the covariates on the hazard, we used the conventional representation of the Cox proportional hazards model, which means that the hazard ratios have their conventional interpretation

$$h_i(t) = \exp\{\gamma(t)' X(t)\}\, h_0(t).$$

Time-dependent exposures were allowed to influence the risk in a given observational interval only if the exposure could reasonably be expected to affect the subject for at least half of the length of the interval. Observation intervals beyond advanced islet autoimmunity positivity did not contribute to the analyses. Random effects for family were introduced to accommodate dependence among siblings, and these were assumed to follow a normal distribution with mean zero and with variance estimated from the data.

Web Figure 2. Estimated Log-Hazard and Hazard Functions for Advanced Islet Autoimmunity, DIPP Nutrition Study, Finland.



Web Table 1. Characteristics and Unadjusted Hazard Ratios (HR) and 95% Confidence Intervals (95% CI) for Progression to Type 1 Diabetes in 975 Children With Persistent Islet Autoimmunity, DIPP Nutrition Study, Finland, 1996-2015.

Characteristic	Children With Persistent Islet Autoimmunity (*n* = 975)	Progression to Type 1 Diabetes (*n* = 154)		
		No.	HR	95% CI
Child sex				
Boys	537	96	1.35	0.98, 1.87
Girls	438	58		
P value				0.07[a]
HLA-DQB1risk[b]				
High	221	50	1.67	1.19, 2.33
Moderate	754	104	1	
P value				0.003[a]
Familial type 1 diabetes				
Yes	78	24	2.03	1.31, 3.14
No	875	128	1	
Missing	22	2		
P value				0.002[a]
Maternal vocational education[c]				
None	79	10	1	
Vocational school or course	241	33	1.15	0.57, 2.34
Secondary vocational education	414	58	1.20	0.61, 2.34
University studies or degree	223	50	1.98	1.01, 3.91
Missing	18	3		
P value				0.02[a]
Maternal age, years[c]				
<25	167	24	1	
25-29	332	55	1.29	0.80, 2.09
30-34	281	41	1.18	0.71, 1.95
≥35	195	34	1.33	0.79, 2.24
P value				0.70[a]
Gestational age, weeks				
Q_1 <38.9	219	45	1.41	0.91, 2.17
Q_2 38.9–39.9	251	34	0.98	0.62, 1.55
Q_3 40.0–40.8	225	33	1.05	0.66, 1.68
$Q_4 \geq 40.9$	266	38	1	
Missing	14	4		
P value				0.31[a]
Ponderal index[d]				
$Q_1 < 26.1$	239	40	1	
Q_2 26.1–27.7	238	44	1.11	0.72, 1.71
Q_3 27.8–29.3	252	38	1.00	0.64, 1.56
$Q_4 \geq 29.4$	233	29	0.75	0.47, 1.22
Missing	13	3		
P value				0.44[a]
Maternal smoking during pregnancy				
Yes	82	12	0.82	0.45, 1.47
No	861	138	1	
Missing	32	4		
P value				0.50[a]
Number of siblings[c], %				
0	441	74	1	

1	281	54	1.23	0.87, 1.75
2 or more	233	24	0.68	0.43, 1.07
Missing	20	2		
P value				0.05[a]

Abbreviations: CI, confidence interval; HLA-DQB1, Major Histocompatibility Complex Class II DQ Beta; HR, hazard ratio; Q_{1-4}, quartile 1-4.

[a]*P* values from Cox regression analysis (Wald test).

[b]High risk genotype *HLA-DQB1(*02/*03:02):* Moderate risk genotypes *HLA-DQB1(*03:02/x); x ≠*02, *03:01,*06:02)*

[c]at the time of birth

[d]Ponderal index was calculated as birth weight in kilograms divided by birth length in meters in 3rd power (kg/m^3).

Web Table 2. Duration of Breastfeeding, Age at Introduction of Foods and Unadjusted Hazard Ratios (HR) and 95% Confidence Intervals (95% CI) for Progression to Type 1 Diabetes in 975 Children with Persistent Islet Autoimmunity, DIPP Nutrition Study, Finland, 1996-2015.

Age (months)	Children With Persistent Islet Autoimmunity	Progression to Type 1 Diabetes		
	n=975	n=154	HR	95% CI
Exclusive breastfeeding				
<0.5	311	47	0.86	0.58, 1.26
0.5–2.99	342	56	0.90	0.63, 1.31
>2.99	321	51	1	
Missing	1	0		
P value				0.72[a]
Any breastfeeding				
<5.0	314	46	0.81	0.55, 1.20
5.0–9.0	322	56	1.04	0.72, 1.50
>9.0	329	51	1	
Missing	10	1		
P value				0.40[a]
Cow's milk[b]				
< 0.9	317	49	0.90	0.61, 1.32
0.9–4.0	339	55	0.88	0.61, 1.28
>4.0	316	50	1	
Missing	3	0		
P value				0.77[a]
Fruits or berries				
<3.5	249	41	1.06	0.70, 1.62
3.5–4.0	392	68	1.18	0.81, 1.72
4.0	319	43	1	
Missing	15	2		
P value				0.66[a]
Roots[c]				
<3.0	165	29		
3.0–4.0	606	99	1.11	0.66, 1.88
>4.0	190	24	1.09	0.71, 1.69
Missing	14	2	1	
P value				0.91[a]
Wheat, rye, oats or barley				
<5.0	143	19	0.82	0.48, 1.40
5.0–5.5	567	95	1.05	0.73, 1.53
>5.5	248	37	1	
Missing	17	3		
P value				0.58[a]
Egg				
<8.0	216	44	1.41	0.93, 2.12
8.0–11.0	420	64	1.07	0.73, 1.57
>11.0	310	43	1	
Missing	29	3		
P value				0.21[a]
Meat				
<5.0	68	12	1.03	0.56, 1.91
5.0–5.5	576	93	1.00	0.72, 1.41
>5.5	314	46	1	
Missing	17	3		
P value				0.99[a]

Solid foods[d]				
< 3.0	232	37	1.01	0.60, 1.70
3.0–4.0	563	94	1.18	0.75, 1.87
> 4.0	166	21	1	
Missing	14	2		
P value				0.61[a]

Abbreviations: CI, confidence interval; HR, hazard ratio;

[a]*P* values from Cox regression analysis (Wald test);

[b]Cow's milk includes cow's milk based infant formulas as well as any other foods including cow's milk.

[c]Roots include carrots, potatoes and turnips

[d]Solid foods include roots, fruits or berries, cereals, meat, fish, egg, cabbage, spinach, beetroot and lettuce.

Web Table 3. Unadjusted Hazard Ratios (HR) and 95% Confidence Intervals (95% CI) for Advanced Islet Autoimmunity and Type 1 Diabetes According to Duration of Breastfeeding in Quarters in Children With Increased Genetic Susceptibility for Type 1 Diabetes, DIPP Nutrition Study, Finland, 1996-2015.

Age (months)	Advanced Islet Autoimmunity		Type 1 Diabetes	
	HR	95% CI	HR	95% CI
Exclusive breastfeeding				
< 0.23	1.20	0.85, 1.69	0.77	0.50, 1.19
0.23–1.37	1.61	1.15, 2.23	1.07	0.72, 1.58
1.38–3.5	1.47	1.06, 2.02	0.85	0.56, 1.28
> 3.5	1		1	
P value	< 0.001[a]		0.39[b]	
Any breastfeeding				
< 3.5	1.31	0.96, 1.80	0.89	0.59, 1.35
3.5–6.9	1.37	1.01, 1.86	1.10	0.74, 1.64
7.0–10.5	0.99	0.72, 1.36	0.83	0.54, 1.25
> 10.5	1		1	
P value	< 0.001[a]		0.56[b]	

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]*P* values are from piecewise linear log-hazard survival model (Log likelihood test);

[b]*P* values are from Cox regression analysis (Wald test);

Web Table 4. Food Diversity at Age of 3,4, 6, and 12 Months and the Unadjusted Hazard Ratios (95% Confidence Intervals) for Progression to Type 1 Diabetes in Children With Persistent Islet Autoimmunity, The DIPP Nutrition Study, Finland, 1996-2015.

No. of Food Items[a]	Children With Persistent Islet Autoimmunity (*n*=975)	Progression to Type 1 Diabetes (*n*=154)		
		No.	HR	95% CI
3 months				
0	265	43	1.25	0.82, 1.92
1–2	459	74	1.14	0.77, 1.68
>2	249	37	1	
Missing	2	0		
P value			0.59[b]	
4 months				
0	110	17	1.20	0.69, 2.08
1–2	166	21	0.97	0.60, 1.58
3–4	329	58	1.27	0.88, 1.81
>4	368	58	1	
Missing	2	0		
P value			0.52[b]	
6 months				
0–4	67	9	0.78	0.33, 1.83
5–6	132	21	1.08	0.66, 1.76
7–8	486	76	1.06	0.74, 1.51
>8	288	48	1	
Missing	2	0		
P value			0.89[b]	
12 months				
0–7	56	10	1.63	0.76, 3.51
8–9	134	22	1.29	0.78, 2.14
10–11	444	76	1.34	0.94, 1.90
>11	339	48	1	
Missing	2	0		
P value			0.33[b]	

Abbreviations: CI, confidence interval; HR, hazard ratio;

[a]The food diversity is the sum of the following 13 foods/food groups that the child had started to consume: cow's milk or cow's milk based infant formula (combined); potato; carrot; turnip; fruits or berries (combined); cereals (rye, wheat, oats, or barley combined); other cereals; meat; fish; egg; cabbage; spinach or beetroot (combined); and lettuce and was categorized in tertiles or quartiles.

[b]*P* values are from Cox regression analysis (Wald test)

References

1. Collet D. *Modelling Survival Data in Medical Research*, 2nd ed, Chapman&Hall/CRC 2003: 286-291)